

REMARKS

Claims 1-53 were pending in this case. In the Office Action, several items were discussed. The following Remarks I through VIII are in response to the discussed items:

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I. The Examiner suggested that the title be changed to "N-Benzyl and N-Pyridinylmethyl Pyrazolopyrimidines as Cyclin Dependent Kinase Inhibitors". While the Applicants sincerely appreciate the Examiner's suggestion, it is respectfully pointed out that the invention disclosed herein is more than just N-benzyl and N-pyridinylmethyl pyrazolopyrimidines. Thus, it is concerning to the Applicants that limiting the title as suggested could be too much of a limitation. Applicants are, therefore, leaving the title as filed without change.

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II. Claims 1, 2, 4-9, 14-26 and 31-42 were rejected under 35 U.S.C. § 112, second paragraph, for use of the terms "heteroarylalkyl", "heteroarylalkenyl", and "heterocycloalkyl". The present amendment makes that rejection moot. Withdrawal of the under 35 U.S.C. § 112, second paragraph rejection is, therefore, respectfully requested.

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III. Claims 1-9 and 32-43 were rejected under 35 U.S.C. § 112, second paragraph. It is stated that the variable "p" is not used. The present amendment makes that rejection moot. Withdrawal of the §112, second paragraph rejection is, therefore, respectfully requested.

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IV. Claims 32-36 and 38-40 were rejected under § 112, second paragraph, as being indefinite. The use of the phrases "a patient in need of" and "inhibiting one or more cyclin dependent kinases" was objected to. The term "a patient in need of" is deleted in this amendment. As far as "inhibiting one or more cyclin dependent kinases" ("CDKs") is concerned, the specification provides not only an enormous number of compounds inhibiting the CDKs, but page 359 onwards provides assays of how to measure the inhibitive effect of the compounds on CDKs and Table 87 (page 360) provides the IC50 of representative compounds of the invention. Thus, there is plenty of support for the inhibitory effect of the inventive compounds. As the Examiner points out,

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the specification does provide a representative list of diseases associated with CDKs.

Furthermore, the cyclin dependent kinases (CDKS) are key regulators of the cell cycle. In mammalian cells, entry into S-phase, control of DNA synthesis and ultimately cell division at mitosis are under the control of these

enzymes. Activity of the CDKs is rate limiting for entry into S-phase. Commencement of S-phase is negatively regulated by the retinoblastoma tumor suppressor gene product, Rb. Rb itself regulates the activity of the E2F family of transcription factors. E2F target gene expression is essential for onset of DNA synthesis and entry into the cell cycle. Phosphorylation of Rb by the CDKs releases the repression of E2Fs and allows DNA synthesis to commence. This particular pathway contributes to the so-called "Restriction Point" hypothesis. Hence, CDK activity is required to phosphorylate Rb and drives entry into the cells cycle. These data predict that a key phenotype observable following CDK inhibition will be cell cycle arrest. This is readily observable in a variety of assays.

The CDKs also play key roles during late S-phase wherein the activities of CDK2 and CDK1 in association with cyclin A are required to suppress the transcriptional activity of E2F, thus signaling the end of DNA synthesis. Prolonged and inappropriate activation of the E2Fs during this stage of the cell cycle is correlated with the onset of apoptosis. Hence, in asynchronously growing populations of tumor cells, failure to down-regulate E2F activity during late S-phase is expected to induce apoptosis. Therefore, another key phenotype anticipated following CDK inhibition is apoptosis. Both cell cycle arrest and onset of apoptosis should be correlated with the complete inhibition of CDKs, and subsequent dephosphorylation of the Rb tumor suppressor protein. Thus, potent and selective inhibitors of CDK2 and CDK1 are expected to suppress phosphorylation of Rb.

The connection between the inhibition of CDKs and various diseases has been supported by several authors. In fact, Fischer, *Expert Opinion on Investigational Drugs* (June 2003) that the Examiner has pointed out in another section of the Office Action, states (on page 965 right hand column, line 3 onwards):

“Clearly, CDK inhibitors continue to hold much promise as a new modality in the treatment of cancer, despite the recent realisation that CDKs regulate important physiological functions that are not directly related to cell-cycle progression. Furthermore, it is becoming increasingly clear that CDK inhibitors may find clinical application in proliferative diseases other than cancer, particularly inflammatory disorders. For example, ROS was shown to suppress the proliferation of mesangial cells and nephron tubule podocytes, New understanding of CDK biology, particularly as far as the functions of certain CDKs in the regulation of transcription and neuronal functions are concerned, have provided novel biomedical rationales for yet additional indications. Particularly exciting is the prospect that CDK inhibitors may provide novel antiviral agents”.

Thus, the authors point out that CDK inhibitors are not only a “treatment of cancer” but also “may find clinical application in proliferative diseases other than cancer etc. Applicants would like to point out that this is an exciting, evolving area of research. Applicants have provided several compounds with excellent CDK inhibitory activity that could be useful not only in the various diseases that are listed in the specification but are also currently under investigation by various researchers. Withdrawal of the §112, second paragraph rejection is, therefore, respectfully requested.

V. Claims 1-53 were rejected under 35 U.S.C. §112, second paragraph, for use of the term “solvates”. Applicants would like to point out that while the specification may not necessarily provide working examples of solvates, it provides sufficient description of solvates. Applicants thus believe that there is sufficient support for “solvates” in the specification. However, in the interest of advancing the prosecution, the term “solvate” is now removed from the claims, as suggested by the Examiner.

VI. Claims 32-42 were rejected under 35 U.S.C. § 112, first paragraph. It is stated that the specification “does not reasonably provide enablement for treating any human disease.” As stated previously, the invention discloses a very large number of compounds, an assay to measure the CDK inhibitory activity as well as the activity (IC50) of a *representative* number of compounds. The Examiner cites the *Fischer* article (*Expert Opinion on Investigational Drugs*) referred to above, and states that the CDK inhibitor flavopiridol failed to show anti-tumor efficacy, 7-hydroxystaurosporine failed to show adequate PK properties, roscovitine had not been tested in efficacy

trials, BMS-387032 had only been studied in Phase I, and states "recent reports have questioned the validity of CDK2 as a good target for ... cancer." Applicants respectfully traverse the rejection for reasons stated below:

As discussed above under Section IV, and without repeating everything stated therein, Applicants believe that CDKs do indeed play a role in the regulation of tumor cell progression and cancer. This fact, again as stated above, is acknowledged in the *Fischer* article cited by the Examiner, as well as by several other authors. Thus, for example, B. Hu et al, *Molecular and Cellular Biology*, Vol. 21 (8), 2755-2766 (2001) (**EXHIBIT I**) state (page 2755, left hand column): "Addition of Cdk2 inhibitors... can block initiation of DNA synthesis. Evidence of amore limited scope suggests additional potential roles for Cdk2 in later cell cycle events."

S. van den Heuvel, *Science*, Vol. 262 (December 24, 1993) page 2050 (**EXHIBIT II**) states (see Abstract on page 2050): "...Cdk3, in addition to Cdc2 and Cdk2, executes a distinct and essential function in the mammalian cell cycle."

Furthermore, as far as flavopiridol (alvocidib) and other compounds are concerned, there are several reports that such compounds are indeed under further study in trials. For example, J. Byrd et al, *Clin. Cancer Res.*, Vol. 11 (11), pages 4176-4181 (2005) (**EXHIBIT III**) state (see *Conclusions* in the Abstract section on page 4176): "Flavopiridol has modest, schedule-dependent clinical activity in relapsed CLL and warrants further investigation utilizing alternative schedules of administration." Also, on page 4180 in the same article, the authors state:"... [t]his agent remains a worthwhile therapy to develop."

EXHIBIT IV is an article by J. brown, *Clin. Cancer. Res.*, Vol. 11 (11), 3971 (2005). On page 3972 (left hand column, 8th line from bottom up) states: "These results, emerging from persistent and careful characterization by Byrd and colleagues, suggest significant activity of flavopiridol in refractory CLL."

EXHIBIT V is a 20-page copy from Iddb3, the data base on investigational drugs (June 1, 2005 update). The article states, on page 10: "Alvocidib's selectivity for cyclin-dependent kinases also makes it a potential therapeutic tool for the treatment of smooth muscle cell rich vascular

lesions..... In vitro studies demonstrated that alvocidib can potentiate the action of many cytotoxic agents including cisplatin, paclitaxel... and 5-fluorouracil.”

EXHIBIT VI is a 14-page copy of an Iddb3 report on seliciclib ((R)-roscovitine) (June 1, 2005 update). On page 1, it states: “Seliciclib... is under development by Cyclacel Ltd for the potential treatment of various cancers and inflammatory diseases Phase IIa trials in non-small-cell lung cancer (NSCLC) and breast cancer were initiated in January 2003. ... In March 2004, clinical trials in mantle cell lymphoma, multiple myeloma (MM) and lymphoid leukemia were initiated.”

EXHIBIT VII is 4-page copy from an Iddb3 report on BMS-387032 (June 1, 2005 update). It states that Bristol-Myers Squibb outlicensed its rights to Sunesis in April 2004, and Sunesis is investigating BMS-387032 (now SNS-032) “for the potential iv or oral treatment of solid and hematological cancers.”

Applicants thus believe that there is ample, well-documented evidence, already published as well as ongoing, that CDK inhibitors are indeed worthwhile targets in the study of cancer. Withdrawal of the 35 U.S.C. §112, first paragraph rejection is, therefore, respectfully requested.

VII. Claims 1, 2, 4-8, 16, 19, 41 and 43 stand rejected under 35 U.S.C. §102(b) as being anticipated by *O'Brien*. Claims 1-10, 19, 23, 40 and 42 were rejected under 35 U.S.C. §102(b) as being anticipated by *Hirai*. Claims 1, 4-8, 15, 19 and 42 were rejected under 35 U.S.C. §102(b) as being anticipated by *Ruhter*. The present amendment makes that rejection moot. Withdrawal of the 35 U.S.C. §102(b) rejections is, therefore, respectfully requested.

VIII. Claims 1-28 and 32-43 were rejected under 35 U.S.C. §101, provisional double patenting, over claims 1-29 and 31-42 of copending, co-owned, patent application, Serial No. 10/654,546. Separately, claim 29-31 were provisionally rejected under obviousness-type double patenting over claim 30 of the same copending case. Applicants have amended the present

case; it is believed that the conflicting scope is now removed. Withdrawal of the double patenting rejections is, therefore, respectfully requested.

IX. New claims 54-70 have been added. There is sufficient support on
5 various pages in the specification. Thus, no new matter has been added.

There being no other rejections pending, Applicants believe that claims 31-70 are in allowable condition and such an action is earnestly solicited.

If the Examiner has any questions, the Examiner is invited to contact the undersigned.

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